

REMARKS

Claims 1-14, 17-21, and 43-92 are pending in the application, claims 84-92 having been added. Claims 8, 45, 50, 55, 60, 64, 69, 75, and 80 have been amended. New claims 84-92 recite limitations previously contained in claims 8, 45, 50, 55, 60, 64, 69, 75, and 80. No new matter has been added by these amendments.

35 U.S.C. § 112, Second Paragraph

Claims 8, 45, 50, 55, 60, 64, 69, 75, and 80 were rejected as allegedly indefinite. On pages 2-3 of the Office Action, the Examiner stated that "[a] broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired." According to the Examiner, the claims rejected under this heading "recite the broad recitation chaperone, and the claims also recite chaperonin which is the narrower statement of the range/limitation."

Claims 8, 45, 50, 55, 60, 64, 69, 75, and 80 have been amended to remove the recitation of "chaperonin" and several hsp's. This amendment does not affect the scope of any of these claims. New claims 84-92 have been added that further define the multi-ligand binding receptor of claims 8, 45, 50, 55, 60, 64, 69, 75, and 80 as a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100. In light of these amendments, applicants request that the Examiner withdraw the rejection.

35 U.S.C. 103(a)

Claims 1-14, 17-21, and 43-83 were rejected as allegedly obvious over Brusic et al. (1998) Nucleic Acids Res. 26:368 ("Brusic") in view of Jeff Seale (The GroEL Protein Interaction Database) ("Seale"), and further in view of Flanagan et al., U.S. Patent No. 5,795,734 ("Flanagan") and Duan et al. (1995) Proc. Natl. Acad. Sci. USA 92:6459 ("Duan").

Independent claims 1-5 and the claims that depend therefrom are directed to a ligand profile which is a reproducible characteristic of a given cell, wherein the ligand profile comprises a representation of at least ten different polypeptide ligands, all of which bind to a single type of multi-ligand binding receptor. The claimed invention makes use of the promiscuous binding

properties of multi-ligand binding receptors so as to create a polypeptide profile that is characteristic of a given cell. The application also includes claims directed to methods of generating and using ligand profiles. Applicants respectfully submit that nothing in any of the cited references, either alone or in combination, describes or suggests the ligand profiles and methods of the invention. The four cited references have the common feature of characterizing a protein (or a class of proteins) by describing one or more polypeptides or peptides that interact (directly or indirectly) with the protein. However, none of the four references describes or suggests characterizing a cell by means of creating a profile of polypeptide ligands. The references are addressed in the order that they were raised by the Examiner.

On pages 3-4 of the Office Action, the Examiner stated that

Brusic et al. disclose a database of MHC-binding peptides, wherein MHC is class I or class II. Such a database is interpreted as being equivalent to a serial of profiles, as required in the instant claims. The disclosed profile of MHC class I receptor is characteristic of T-cell (see page 369, left column). Each individual ligand is characterized based on at least three of the chemical or biological attributes including peptide sequence, MHC specificity, activity, binding affinity, source protein and anchor position, and at least 4617 peptides are represented for MHC class I receptor in the profile (see page 368, Abstract and page 371, Table 2), as required in the instant claims. These at least 6 attributes make obvious of the "at least three" or "at least two" or "at least one" attributes, as required by the instant claim 1, or claim 2 or claim 3, and the claims dependent from claims 1-3.

The MHCPEP database of Brusic is not a ligand profile that is a reproducible characteristic for a given cell. Brusic's database contains a description of over 13,000 peptide sequences that have been found to bind to a wide variety of MHC class I or class II molecules. Brusic's database constitutes a profile of MHC binding peptides, but provides no characterization whatsoever of a cell that may contain either the peptides or their corresponding proteins. Brusic's database is an attempt to describe the universe of peptide sequences that are capable of binding to MHC molecules. The database contains MHC-binding data both for peptides that correspond to portions of naturally occurring proteins as well as for mutant peptides that have no naturally occurring counterpart (see, e.g., Brusic, page 369, column 2). Brusic's extensive characterization of MHC-binding peptides is said to be useful in that it "facilitates

building of predictive models for determination of novel T-cell epitope candidate peptides” (Brusic, page 370, column 2).

Contrary to the Examiner's assertions on page 4 of the Office Action, the compilation of MHC-binding peptides in Brusic's database does not represent a profile characteristic of a T cell (or any other cell). The compilation of peptides presented by Brusic is nowhere described as or suggested to be representative of any particular cell or cell type, T cell or otherwise. In fact, because a common means for detecting MHC-peptide interactions entails the use of synthetic peptides and purified MHC molecules, “cellular context” is not even a relevant concept for many of the peptides described by Brusic. Because the peptides described by Brusic are not collectively representative of any cell, they do not constitute a “ligand profile” of the claimed invention. Furthermore, Brusic's collection and description of peptide sequences that can bind to MHC molecules provides no motivation whatsoever to create a profile of polypeptide ligands, MHC ligands or otherwise, that is a reproducible characteristic of a cell. Although Brusic provides a motivation to catalogue peptide sequences that can bind to MHC molecules, the reference provides no motivation to create a ligand profile for a given type of cell.

At page 5 of the Office Action, the Examined stated that

Brusic et al. do not disclose ligand profiles for receptors that are not an MHC class I or MHC class II receptors, but motivate combining data from different sources and linking the databases with other databases. Jeff Seale disclose a ligand profile for a chaperonin protein GroEL comprising 31 ligand proteins, which GroEL is not an MHC class I or MHC class II receptors, but a chaperonin, as required by the instant claims. The profile comprises at least three chemical or physical attributes including ligand name, release requirements and reference number (see pages 1-4).

Similar to the MHCPEP database of Brusic (which catalogues MHC-binding peptides), Seale catalogues proteins that have been described as being GroEL substrates; and like the MHCPEP database of Brusic, the proteins catalogued by Seale do not constitute a reproducible ligand profile for a given cell. Rather, Seale presents a compilation of documented GroEL substrates, unassociated with a cellular context (if any) in which such an interaction was characterized. In fact, the proteins listed by Seale are derived from a wide variety of species, thereby clearly precluding the collection of proteins from constituting a ligand profile for any

given cell. For these reasons, the listing of GroEL substrates by Seale is not collectively representative of any cell, and therefore does not constitute a "ligand profile" of the claimed invention. Furthermore, Seale's attempt to catalogue GroEL substrates provides no motivation to profile a cell by means of polypeptide ligands that bind to GroEL or any other protein.

As described above, and contrary to the Examiner's assertions, neither Brusic nor Seale provides any motivation for generating a ligand profile for a given cell. These references are directed to characterizing those polypeptides that can bind to MHC molecules (Brusic) or GroEL molecules (Seale), with no limitation as to how many types of cells are represented. There is no suggestion whatsoever that a database should be constructed that catalogues the particular repertoire of polypeptide ligands that bind to an MHC or a GroEL molecule in a given cell or cell type.

At pages 5-8 of the Office Action, the Examiner alleged that the ligand profiles and methods of the claimed invention are obvious in light of the disclosures of Flanagan and Duan together with Brusic and Seale.

Flanagan describes the discovery of a novel EPH receptor ligand termed Elf-1. Flanagan describes methods of forming and detecting complexes between an EPH receptor and Elf-1 polypeptides (column 38, line 45, to column 39, line 8, as cited by the Examiner).

Duan describes a series of experiments designed to identify proteins that associate with the von Hippel-Lindau (VHL) tumor suppressor gene product. These associated proteins were characterized as follows: an epitope tagged version of a recombinant VHL protein was produced in COS cells; the COS cell proteins were labeled with ³⁵S; the epitope tagged VHL protein was immunoprecipitated from a COS cell lysate; and proteins that coimmunoprecipitated with the epitope tagged VHL protein were analyzed by a combination of gel electrophoresis and autoradiography.

The experiments described by Flanagan and Duan neither disclose nor suggest the claimed ligand profiles and methods of creating and using such profiles. These references are directed to characterizing proteins and polypeptides that bind to the EPH receptor (Flanagan) or VHL protein (Duan). The references provide no motivation to construct a profile of a cell by creating a profile of polypeptide ligands that bind to a multi-ligand binding receptor.

In analyzing the Duan reference, the Examiner stated on page 7 of the Office Action that “[i]t is noted that due to the broad meaning of the terms ‘receptor,’ ‘ligand’ and ‘profile’, the protein VHL is interpreted as a receptor, and the proteins it binds to are interpreted as ligands. The gels containing different ligands after fractionation are interpreted as profiles.”

Applicants submit that Duan’s gels containing polypeptides that coimmunoprecipitate with the VHL protein are not ligand profiles as claimed in this application.

First, there is no indication that VHL is a “multi-ligand binding receptor,” which is defined in the application (at page 10, lines 1-6) as a polypeptide that reproducibly binds to a particular set of at least ten different proteins or peptides in or derived from a given animal cell. Duan indicates that seven VHL-associated proteins were detected in the coimmunoprecipitation experiments described therein (see seven arrowheads of Figs. 2B and 2D on page 6461 of Duan). Furthermore, Duan gives no indication as to whether the coimmunoprecipitated polypeptides bound directly to VHL or were merely part of a complex that included at least one VHL-binding protein. The claimed ligand profiles must include a characterization of at least ten different polypeptide ligands, all of which bind to a single type of multi ligand binding receptor.

Second, Duan analyzes proteins bound to the VHL protein based upon their apparent molecular weight as determined by gel electrophoresis. Merely disclosing the molecular weight of a group of proteins that coimmunoprecipitate with another protein in a cell lysate does not constitute a ligand profile of the claimed invention. Additionally, and contrary to the Examiner’s assertions on page 6 of the Office action, Duan provides no chemical or physical description of the VHL-associated proteins other than their molecular weights (which applicants consider to be the same as the “sizes” of the proteins). Charge, pH, and sequence of the VHL-associated proteins are not disclosed by Duan.

The claimed ligand profiles have defined requirements as to the nature of the characterization of the polypeptide ligands. Specifically, the ligand profiles of claims 1-5 require the characterization of each of at least ten different polypeptide ligands based upon: at least three physical or chemical attributes (claim 1); at least two physical or chemical attributes, including mass or mass-to-charge ratio (claim 2); at least one physical or chemical attribute, including amino acid sequence (claim 3); ion fragmentation patterns (claim 4); or amino acid sequences (claim 5). Neither Duan nor Flanagan discloses creating such ligand profiles. The

Examiner apparently does not contest this fact, as the present rejection is for alleged obviousness, not anticipation. However, the Examiner has cited no motivation in the references that would lead one of skill in the art to generate a profile that meets the requirements of the claimed invention. As described previously, Brusica and Seale did not suggest the cataloguing of a repertoire of polypeptide ligands that bind to a multi-ligand binding receptor in a given cell or cell type. Nothing in Flanagan or Duan cures this deficiency.

In summary, each of the four cited references describes the characterization or detection of molecules that bind to a particular protein or class of proteins, as follows: MHC molecules (Brusica); GroEL molecules (Seale); EPH receptor (Flanagan); and VHL protein (Duan). However, none of these references suggests using a multi-ligand binding receptor to create a ligand profile for a given cell, as is required by the pending claims. In light of these deficiencies, applicants submit that the references alone or in combination do not render the claimed invention obvious. Applicants therefore request that the Examiner withdraw the rejections.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested. Attached is a marked-up version of the changes being made by the current amendments. The attached page is captioned "Version with markings to show changes made."

Applicant : Roman M. Chicze
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Page : 11

Attorney's Docket No.: 08191-008003

Enclosed is a check for excess claims fees, a Petition for Extension of Time, and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-008003.

Respectfully submitted,

Date: September 24, 2001

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Version with Markings to Show Changes Made

In the Claims:

Claims 8, 45, 50, 55, 60, 64, 69, 75, and 80 have been amended as follows:

8. (Amended) The ligand profile of claim 1, wherein the multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

45. (Amended) The ligand profile of claim 2, wherein the multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

50. (Amended) The ligand profile of claim 3, wherein the multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

55. (Amended) The ligand profile of claim 4, wherein the multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

60. (Amended) The ligand profile of claim 5, wherein the multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

64. (Amended) The method of claim 10, wherein the selected type of multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

69. (Amended) The method of claim 14, wherein the first type of multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

75. (Amended) The method of claim 17, wherein the given type of multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.

80. (Amended) The set of ligand profiles of claim 21, wherein the at least one type of multi-ligand binding receptor is a chaperone, [a chaperonin,] a calnexin, a calreticulin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, [hsp60, hsp65, hsp70, hsp90, hsp25,] an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, [hsp100,] a proteasome, a trafficking protein, or a retention protein.